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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/192,167	11/13/1998	THOMAS J. MEADE	A-67412/RFT/	9443

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EXAMINER

CRANE, LAWRENCE E

ART UNIT	PAPER NUMBER
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1623

DATE MAILED: 04/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/192,167

Applicant(s)

MEADE ET AL.

Examiner

L. E. Crane

Art Unit

1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11/10/2003 (amdt E).
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2,3,6,7,10 and 16-29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2,3,6,7,10 and 16-29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Claims 1, 5, 8-9, 11-15 have been cancelled, new claims 22-29 have been added, and claims 2-4, 7, 10, 17 and 19-21 have been amended as per the amendment filed November 10, 2003.

Claims 2-4, 6-7, 10 and 16-29 remain in the case.

Examiner has carefully reviewed the instant amended claims and finds that applicant has again failed repeatedly to demonstrate

- i) a fundamental understanding of the distinction between an organic compound and a substituent structurally related thereto, and
- ii) the distinction between an intermediate compound and a transition state.

The second problem is particularly well illustrated by the errors noted below in claims 22 and 23. The sequence I -> II -> III must either require oxidation followed by reduction, or require that a 2'-pentavalent carbon be present in the "cyclized intermediate."

Applicant has responded to examiner's criticism of the Meade declaration with quotation from the disclosure, the statute, the MPEP and a prior court decision, and with amendments to the claims to specify

2, 2'- or 2, 3'-anhydronucleoside starting materials. However, while the additions are an improvement, the supplied numeric designations are insufficiently descriptive by themselves because the actual structures found in the disclosure (Figures and the sole enabling embodiment at pages 26-27) are uniformly 2, 2'- and 2, 3'-anhydropyrimidine nucleosides. Applicant has not provided an adequate written description in support of anything but 2, 2'- and 2, 3'-anhydropyrimidine nucleosides.

The disclosure is objected to because of the following informalities:

Incorporation by reference of essential material by reference to any patent or any publication inserted in the portion of the specification which describes the invention is improper, except for benefit and parent applications. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by applicant, or a practitioner representing applicant, stating that the amendatory material consists of the same material incorporated by

reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCAP 1973); *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The attempt to incorporate subject matter into this application by reference to patents and other publications at page 4, line 16; p. 5, lines 4-5; p. 7, lines 15-16; p. 9, lines 11 and 14; p. 10, lines 4-5, 9 and 13; p. 12, lines 10-11; p. 14, lines 9-10 and 23-24; p. 19, lines 7, 9 and 22; p. 21, lines 21-22; and p. 26, lines 7 and 11-12 is improper because it is unclear which part(s) of each patent or publication is essential to the execution of the claimed invention, and because patents and or publications may not be available to the ordinary practitioner seeking to reproduce the instant subject matter if issued and/or subsequent to expiration as prior art.

In each of the above cases, the incorporations are of the complete document, and fails to properly point out the particular portions of the US patent(s) being incorporated; see MPEP §608.01(p)(1)(A) noting *In re de Seversky* and in the same paragraph (column 2 of p. 600-769, August 2001 edition) the instruction which reads as follows: “[p]articular attention should be directed to specific portions of the referenced document wherein the subject matter being incorporated may be found.”

In addition, each of the above incorporations represents a failure to provide specific disclosure of how to make and/or use. Therefore, the above citations of the *Hawkins* decisions continue to apply to all incorporations by reference.

Appropriate correction is required.

Applicant’s arguments filed November 10, 2003 have been fully considered but they are not deemed to be persuasive.

Applicant argues that the references incorporated are required because from applicant’s point of view they do not include “essential material.” If this is the case, then applicant should have no problem with removal of the “incorporation by reference” language because by applicant’s own admission (p. 16, lines 4-5, Response of 11/10/2003) the incorporations by reference are ... “non-essential.” Or, applicant may amend the disclosure by moving the noted

incorporations to the "Background" portion of the specification wherein incorporation by reference is not limited. Alternatively, if applicant insists on maintaining the present locations of the noted incorporations by reference, then applicant must provide the requisite declarations and associated amendments provided for by the *In re Hawkins* decisions specifically noted above.

Complete compliance is again respectfully requested.

The disclosure is objected to because of the following newly observed informalities:

In applicant's amendment to the specification at page 27, line 13, applicant is requested to note line 9 of the paragraph wherein the chemical formula "CH₃Cl₂" has been provided. This formula includes a pentavalent carbon, and/or a typographical error. Did applicant intend the formula for the well known solvent methylene chloride (-- CH₂Cl₂ --)?

Appropriate correction is required. Examiner further suggests careful review of the disclosure for similar valence and other typographical errors in chemical formulas.

Claims **2, 3, 7, 10 and 18** are objected to because of the following informalities:

In the claims, terms wherein a location is specified (e.g. "3' position" and "2' modified nucleoside" in claim **2** are incomplete and should read as follows: -- 3'-position -- and -- 2'-modified nucleoside --. This type of error occur repeatedly throughout the claims including six times in claim **10**. In addition in claim **10** at lines 7-8, the term "2,2' and 2,3 anhydronucleosides" only specifies a sugar-base bond in the first case; i.e. refers to only one "anhydro nucleoside." Did applicant intend the term to read -- 2,2'- and 2,3'-anhydronucleosides -- (emphasis added)?

In claim **18** at line 1 the term "a donor atom ... is selected from the group consisting of nitrogen and oxygen" indicates that only a single donor atom is selected from nitrogen and oxygen. Because the disclosure fails to exemplify the selection of a single donor atom as nitrogen or oxygen and because most ligands include multiple coordinating atoms, it seems more likely that applicant intended the term to read -- **the** donor atoms ... **are** selected from the group consisting of nitrogen and oxygen -- (emphasis added).

Appropriate correction is required.

Claims **2, 3, 7, 10, 16, 18-25 and 28** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim **7** the term “comprising” (**first** and **third** occurrences only) is incorrect in the instant claim because said term implies that the chemical structure of the compound/substituent being claimed contains additional structural component(s) not defined in the claim. Applicant is respectfully requested to substitute narrow language such as -- consisting of -- or the like for the noted term. The same problem reoccurs in claim **10** (lines 3 and 4), claim **19** (line 2); claim **20** (line 2); and claim **21** (line 2).

Applicant’s arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Citing precedent, applicant argues that “comprising” is acceptable because it “leaves “the claim open for the inclusion of unspecified ingredients even in major amounts.”” (emphasis added). Examiner respectfully disagrees, noting that the citation is making reference to a mixture of substances, not as in the instant case to a specific chemical compound or generic class of compounds. Applicant is again requested to completely define the structures of the compounds to be made and their starting materials.

Applicant’s argument based on the noted precedent that the need for well defined “metes and bounds” in patent claims is not violated by their use of “comprising” is deemed to be both inappropriately supported by the cited case and also lacking in relevance.

In claim **7**, lines 6-8, the terms “cyclization agent” and “cyclized intermediate” are relatively meaningless unless the details of the chemical reaction being alluded to are provided, thereby rendering this portion of the instant claim lacking in adequately defined metes and bounds.

Applicant’s arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Again applicant is respectfully requested to fill in the details so that the functional language is making reference to specific compounds or specific generic structures. Examiner refers applicant to rejections of claims **22 and 23** below for questions concerning the meaning of "cyclized intermediate." The noted rejection makes plain why it is necessary to clearly and completely define the meaning of chemical structures.

Claim **2** provides for the use of an undefined chemical reagent to introduce a "phosphoramidite group" but, since the claim does not set forth any step(s) involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not deemed to be persuasive.

Applicant argues that "one of ordinary skill in the art would know the steps involved in the the process" Examiner notes that applicant has admitted that "steps" are involved in the claimed process and therefore wonders when applicant will add the requested details to the instant claim to permit the claimed process to be completely defined, so that the ordinary practitioner will not have to guess the metes and bounds of the claimed subject matter.

In claim **3**, adding a phosphoramidite-derivatized nucleoside to the terminus of a "growing" nucleic acid appears to make reference to the Caruthers process of nucleic acid synthesis, but remains incomplete for failure to specify the structural variables which define the complete chemical structural formula of the "phosphoramidite modified nucleoside."

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

The noted terminology fails to provide a complete description of what particular step or steps are being executed to effect the "incorporation. Applicant is again respectfully requested to provide a complete claim.

Claim **3** provides for the use of a 3'-phosphoramidite derivative of a 2'-modified nucleoside in a process wherein same is incorporated into an oligonucleotide but, since the

claim does not set forth any step(s) involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant is referred to the response following the preceding rejection of claim 2.

Claim 10 contains nearly all of the same problems defined above for claim 7. The term "a covalently attached polydentate ligand" only hints at the structure of the intended product.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant responds to the rejections of this claim beginning at page 22 of the response and cites precedent in support of the use of "comprising." However, applicant's arguments totally ignore the fact that the instant process claims are not directed to *compositions* wherein comprising is appropriate, but are directed to specific compounds as starting materials and as products wherein the structural details of said compounds are critical to establish both metes and bounds and to avoid overlap with the prior art. Applicant is also referred to the response following the rejection of claim 7 above.

In claim 19 at lines 2-3, the term "transition metal ion is chelated by said polydentate ligand comprising a primary amine and pyridine" is confusing at best and contains several technical errors. The included terms "primary amine" and "pyridine" are names for a separate generic class of compounds and a single separate compound, respectively, but seem to have become structurally incorporated into the "ligand." Clarification is respectfully requested. See also claims 20-21 wherein very similar errors are also present (the terms "primary amine," "bipyridine" and "phenanthroline" each refer to specific separate compounds, not substituents). Again Examiner respectfully suggests the need for complete chemical structures.

Applicant's arguments with respect to claims 19-21 have been considered but are deemed to be moot in view of the new grounds of rejection. Applicant's amendments necessitated this new grounds of rejection.

In claim **18** at lines 1-2, the term “a donor atom of said polydentate ligand is selected from ... nitrogen and oxygen” by its reliance on the highlighted indefinite article does not define which atoms is being referred to and also suggests that other not defined selections are possible with other donor atoms within the ligand. Examiner suggests that the term start with - **the** donor atoms -- as one way of addressing this problem.

Applicant's arguments with respect to claim **18** have been considered but are deemed to be moot in view of the new grounds of rejection. Applicant's amendments necessitated this new grounds of rejection.

In claims **22 and 23** the “cyclized intermediate” (II) is drawn in a manner suggesting that the 2'-sugar carbon has been oxidized from its state in structure (I), and further that transition to structure (III) involves a reduction step. However, neither oxidation nor reduction have been provided for in the instant claimed process. Alternatively, examiner wonders whether the structures labeled (II) in the noted claims are structural representations of -- transition states -- as opposed to “cyclized intermediates,” wherein the latter terms suggests an isolatable chemical substance. See Figures **1, 2 and 3** wherein correct representations of the process steps have been shown.

Applicant's arguments with respect to claims **22 and 23** have been considered but are deemed to be moot in view of the new grounds of rejection. Applicant's amendments necessitated this new grounds of rejection.

In claims **22** (two occurrences), **23** (two occurrences) **and 28** the chemical name “2-cyanoethyl N,N-diisopropylchlorophosphoramidite” incorrectly makes reference to a separate chemical compound, not a substituent.

Applicant's arguments with respect to claims **22, 23 and 28** have been considered but are deemed to be moot in view of the new grounds of rejection. Applicant's amendments necessitated this new grounds of rejection.

In claim **23**, the structure (III) includes a representation at the 2'-position which suggests a schematic diagram as opposed to a chemical formula. The 2'-nitrogen substituent need not necessarily be included as a ligand electron pair donor because many polydentate ligands (e.g.

EDTA) provide sufficient ligand electron pairs to occupy all metal ion orbitals without need to include the attaching amino group as a ligand. Again a complete and accurate chemical formula wherein the ligands and metal ions being used are accurately represented with structural formulas would overcome this confusion or incompleteness.

Applicant's arguments with respect to claim **23** has been considered but are deemed to be moot in view of the new grounds of rejection. Applicant's amendments necessitated this new grounds of rejection.

In claims **16 and 24**, the term "ferrocene" is directed to a compound, not a substituent, and thereby renders the instant claims lacking in proper antecedent basis. Applicant may elect to specify a structural representation which includes a ferrocenyl group to accurately represent the subject matter being claimed.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Again applicant is respectfully requested to clarify the intended structures with complete formulas because applicant has clearly not mastered the terminology in the art sufficiently to avoid even the simplest errors, e.g. misnaming a substituent as its parent compound.

In claim **25** reference to "bases is selected from ... a pyrimidine connected to X at the 2-position and a purine connected to X at the 3-position" is unclear because the locations of the "2-position" and the "3-position" (or is it "2'-position" or 3'-position" ??) have not been specified. Clarification is respectfully requested.

Applicant's arguments with respect to claim **25** have been considered but are deemed to be moot in view of the new grounds of rejection. Applicant's amendments necessitated this new grounds of rejection.

Claims **22-29** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims have not met the written description standard because the instant claims include "intermediates" which appear to have undergone an oxidation and then must undergo a reduction to become the final product, process steps the execution of which are not described in the disclosure.

Applicant's arguments with respect to claims **22-29** have been considered but are deemed to be moot in view of the new grounds of rejection. Applicant's amendments necessitated this new grounds of rejection.

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made."

Claims **2-4, 6-7, 10 and 16-21** are rejected under 35 U.S.C. §103(a) as being unpatentable over **Nexstar '102** (PTO-892 ref. L).

The instant claims are directed to a process for making labelled nucleosides from anhydro-nucleosides wherein the label is an "electron transfer moiety," for making the phosphoramidites thereof, and for making standard or modified oligonucleotides or polynucleotides therefrom via phosphoramidite coupling.

The Nexstar '102 reference discloses processes for making labelled nucleosides from anhydro-nucleosides, for making the phosphoramidites thereof, and for making standard or modified oligonucleotides or polynucleotides therefrom via phosphoramidite coupling including compounds modified by metal-ion-containing coordination complexes (see pp. 9-10 and structure 1 at p. 9). Applicant is referred to pages 17, 21, 23, 26, 3140, 49, 50 and 53, and claim *1*, at p. 59, lines 10-11, and claims **5, 20, 22 and 25** wherein the last three claims disclose the nucleoside starting material, disclose the phosphoramidite analogues of the nucleoside, and imply the use of said phosphoramidites to make oligonucleotides incorporating the modified nucleosides by claiming compounds which could be the product of a phosphoramidite oligonucleotide synthesis.

Teachings of the prior art which disclose in detail subject matter which reads on the invention as claimed is deemed to render the instant claims lacking in patentable distinction in view of the noted prior art.

Therefore, the instant claimed process for making labelled nucleosides from anhydro-nucleosides, for making the phosphoramidites thereof, and for making standard or modified oligonucleotides or polynucleotides therefrom via phosphoramidite coupling, would have been obvious to one of ordinary skill in the art having the above cited reference before him at the time the invention was made.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

The above rejection has been limited to claims which are so functionally defined that overlap with the noted prior art is still deemed to be a properly factual conclusion. Therefore, while applicant argues correctly that the instant specific embodiments are not obvious over the prior art, the claims are so lacking in specificity that the instant rejection is deemed to remain appropriate.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. §1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. §1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Claims **22-29** would be allowable if rewritten or amended to overcome the rejections under 35 U.S.C. 112.

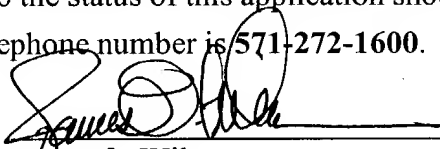
Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX (unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 703-872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at **571-272-0661**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec
04/01/2004


James O. Wilson
Supervisory Patent Examiner
Technology Center 1600